Isopyrazam/Difenoconazole

Isopyrazam/Difenoconazole SC (A21295D) –
***In Vitro* Eye Irritation Test in Isolated Chicken Eyes**

Final Report

DATA REQUIREMENT(S): OECD 438 (2013)
EPA OPPTS 870.2400 (1998)
EC No 440/2008, B.48 (2008)

AUTHOR(S): Barbara Kanizsai, M.Sc.

COMPLETION DATE: 10 February 2016

PERFORMING LABORATORY: CiToxLAB Hungary Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

LABORATORY PROJECT ID: Report Number: 15/419-038CS
Study Number: 15/419-038CS
Task Number: TK0283676

SPONSOR(S): Syngenta Ltd.
Jealott's Hill, International Research Centre
Bracknell, Berkshire, RG42 6EY, United Kingdom

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STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the study plan and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17).

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: Kanizsai Barbara Date: 10 February 2016

Barbara Kanizsai, M.Sc.
Study Director

Performing Laboratory: CiToxLAB Hungary Ltd.
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QUALITY ASSURANCE STATEMENT

Study Number: 15/419-038CS

Study Title: Isopyrazam/Difenoconazole SC (A21295D) - *In Vitro* Eye Irritation Test in Isolated Chicken Eyes

Test Item: Isopyrazam/Difenoconazole SC (A21295D)

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
30 October 2015	Study Plan	30 October 2015	30 October 2015
03 November 2015	Treatment	03 November 2015	03 November 2015
30 November 2015	Draft Report	30 November 2015	30 November 2015
09 February 2016	Final Report	09 February 2016	09 February 2016

Signature: Heidenré Grób Ro Date: 10 February 2016

Ramóna Heidenré Grób, B.Sc.
On Behalf of QA

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MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "Isopyrazam/Difenoconazole SC (A21295D) - *In Vitro* Eye Irritation Test in Isolated Chicken Eyes" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 10 Feb 2016

Alyson Leyshon, M.Sc.
Managing Director

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GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Barbara Kanizsai, M.Sc.	Study Director
David J Esdaile, M.Sc.	Director of Science and Regulatory Affairs
Orovecz Balázs, B.Sc.	Assistant Scientist
Ramóna Heiderné Grób, B.Sc.	Quality Assurance Unit
Claire Elliott	Syngenta Study Managers

Study dates

Study Plan:	02 November 2015
Experimental Starting Date:	03 November 2015
Experimental Completion Date	03 November 2015
Date of Draft Report:	01 December 2015
Date of Final Report:	10 February 2016

Deviations from the Study Plan

There were no deviations during the study.

Performing laboratory test substance reference number

150364

Other

The study documents and samples:
- study plan,
- all raw data,
- sample of the test item,
- original study report and any amendments,
- correspondence
- corneas

will be archived according to the Hungarian GLP regulations and to applicable SOP's in the archives of CiToxLAB Hungary Ltd. 8200 Veszprém, Szabadságpuszta, Hungary. This is for a period of 15 years.
After the retention time of 15 years has elapsed all the archived materials listed above will be returned to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

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1.0 EXECUTIVE SUMMARY

1.1 Study Design

An *in vitro* eye irritation study of the test item isopyrazam/difenoconazole SC (A21295D) was performed in isolated chicken's eyes. The irritation effects of the test item were evaluated according to OECD Test Guideline No. 438 (26th July 2013).

After the zero reference measurements were taken and recorded, the eye was held in a horizontal position and 30 µL of isopyrazam/difenoconazole SC (A21295D) was applied onto the centre of the cornea such that the entire surface of the cornea was covered. After 10 seconds, the surface was rinsed with physiological saline. The positive control eyes were treated in a similar way with 30 µL benzalkonium chloride solution 5 % (w/v). The negative control eye was treated with 30 µL of physiological saline (Salsol solution 0.9%). Corneal thickness, corneal opacity and fluorescein retention were measured and any morphological effects (pitting or loosening of the epithelium) evaluated.

1.2 Results

No significant corneal swelling and no corneal opacity changes were observed during the four hour observation period. No fluorescein retention change was noted. No other corneal effect was observed. The overall ICE class was 3 x I for the test item.

The negative and positive control group results demonstrated that the study was valid and demonstrated the sensitivity of the assay.

1.3 Conclusion

Under the conditions of this *in vitro* eye irritation study in isolated chicken eyes, isopyrazam/difenoconazole SC (A21295D) is concluded to be non-irritant.

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2.0 INTRODUCTION

2.1 Purpose

The Enucleated Eye Test with isolated eyes of chickens is a well validated and accepted *in vitro* test system. It has been recognized as a valuable alternative to the Draize eye irritation test, because it represents a test system nearest to the *in vivo* test, without the need to use live animals. It can also be used as a screening tool for corrosivity/severe irritancy to avoid unacceptable effects *in vivo*. In the Isolated Chicken Eye Test (ICET) the test compound is applied in one single dose onto the cornea of isolated eyes, which are obtained from animals that had been slaughtered for reasons other than toxicity testing.

According to the 26 July 2013 version of the OECD 438 guideline, this method can provide detailed information about the effects of test items on the cornea, and can be used to identify chemicals not requiring classification for eye irritation, or for serious eye damage, as defined by the UN GHS (UN GHS non-classified or UN GHS Category 1). The test is described in OECD 438 and is approved by international regulatory agencies as a partial replacement for the identification of non-irritant, corrosives/severe irritants in the *in vivo* Rabbit Eye Assay (OECD 405).

2.2 Guidelines

The study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

- OECD Guidelines for Testing of Chemicals 438 (adopted on 7th September 2009, updated on 26th July 2013): "Isolated Chicken Eye Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage"

- OPPTS 870.2400 (EPA 712-C-98-195) August 1998

- EU Commission Regulation (EC) No 1152/2010 (8th December 2010) amending, Regulation (EC) No 440/2008: Method B 48. "Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants" Official Journal of the European Union No. L324, dated 09 December 2010.

- INVITTOX (1994) Protocol 80: Chicken Enucleated Eye Test (CEET).

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory. The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. monitored the conduct of the study.

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3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor.

Name:	Isopyrazam/difenoconazole SC (A21295D)
Chemical name:	CGA169374/SYN520453 SC (125/125) A21295D
Batch number:	JHU002-107-007
Product code:	A21295D
Appearance:	Homogenous Off-white Liquid, suspension
Purity:	Considered as 100%
Recertification date:	29 September 2017
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to assure personnel health and safety. Potential to cause serious eye irritation. Suspected of damaging the unborn child. Very toxic to aquatic life.

A Test Item Data Sheet supplied by the Sponsor is given in Appendix 1.

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

3.2 Identification and Receipt

The test item of a suitable chemical purity together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of the test item was made in the Pharmacy Unit of CiToxLAB Hungary Ltd. on the basis of the information provided by Sponsor.

3.3 Test Item Preparation

The test item was applied undiluted. A volume of 30 µL test item was applied to the entire surface of the cornea attempting to cover the cornea surface uniformly with the test substance. A pipette was used for 30 µL test item / eye.

3.4 Test Item Solubility

Solubility of the test item in physiological saline was tested prior to the experiment (30 µL test item in 1 mL physiological saline). The test item did not dissolve in physiological saline (although the test item created a homogenous suspension with the physiological saline).

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3.5 Subsidiary Materials

Positive Control

Test Item:	Benzalkonium chloride solution 50 % in water
Batch number:	SZBC2960V
CAS Number:	63449-41-2
Manufacturer:	Sigma-Aldrich Co.
Expiry date:	25 March 2018
Storage condition:	Room temperature

The benzalkonium chloride solution 50 % in water was mixed with distilled water (Manufacturer: TEVA Co.; Batch number: 2211213, Exp. date: 31 December 2016) to achieve the final concentration of 5% (w/v). The treatment solution was prepared immediately before the experiment.

Negative Control

Name:	Physiological saline (Salsol solution 0.9 %)
Lot number:	51642Y05-1
Manufacturer:	B. Braun Pharmaceuticals AG
Expiry date:	31 March 2018
Storage condition:	Room temperature

Fluorescein retention test

Name:	Fluorescein 10 % (w/v)
Lot number:	13221042
Manufacturer:	Delpharm Huningue SAS
Expiry date:	30 April 2016
Storage condition:	Room temperature

Fluorescein 10 % (w/v) was mixed with physiological saline (Manufacturer: B. Braun Pharmaceuticals AG, Batch number: 51642Y05-1, Expiry date: 31 March 2018) to achieve the final concentration of 2 % (w/v). The resulted solution was stored at room temperature (Dispensary code: S43088, Expiry date: 02 December 2015).

3.6 Chicken Heads Collection and Transport

Strain of chicken:	ROSS 308
Source:	TARAVIS KFT. 9600 Sárvár, Rábasömjéni u 129., Hungary

Chicken heads were collected after being slaughtered in a commercial abattoir from chickens (approximately 7 weeks old) which are used for human consumption.

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Heads were collected by a slaughter house technician. After collection, the heads were inspected for appropriate quality and wrapped with paper moistened with saline, then placed in a sealed plastic box (4-5 heads/box).

The heads were immediately transported to CiToxLAB Hungary Ltd. at ambient temperature. The heads were received at CiToxLAB Hungary Ltd. and processed within approximately 2 hours of collection.

3.6.1 Eyes selection

After removing the head from the plastic box, it was put on soft paper. The eyelids were carefully cut away with scissors, avoiding damaging the cornea. One small drop of fluorescein solution (2 % (w/v)) was applied onto the cornea surface for a few seconds and subsequently rinsed off with 20 mL physiological saline. Then the fluorescein-treated cornea was examined with a hand-held slit lamp or slit lamp microscope, with the eye still in the head, to ensure that the cornea was not damaged. If the cornea was in good condition, the eyeball was carefully removed from the orbit.

3.6.2 Preparation of eyes

The eye ball was carefully removed from the orbit by holding the nictitating membrane with surgical forceps, while cutting the eye muscles with bent scissors. Care was taken to remove the eyeball from the orbit without cutting off the optical nerve too short. The procedure avoided pressure on the eye while removing the eyeball from the orbit, in order to prevent distortion of the cornea and subsequent corneal opacity. Once removed from the orbit, the eye was placed onto damp paper and the nictitating membrane was cut away with other connective tissue. The prepared eyes were kept on the wet papers in a closed box so that the appropriate humidity was maintained.

3.6.3 Eyes examination and acclimatization time

The prepared eye was placed in a steel retainer. The cornea was positioned vertically with the eye in the correct relative position (same position as in the chicken head), taking care to avoid putting too much pressure on the eye by the retainer. Due to the relatively firm sclera of the chicken eyeball, only slight pressure was needed to fix the eye properly. The clamp with the eyeball was transferred to a chamber of the superfusion apparatus.

The retainer holding the eye was positioned in such a way that the entire cornea was supplied with physiological saline dripping from a stainless steel tube, at a rate of approximately 3-4 drops/minute or 0.1 to 0.15 mL/minute. The door of the chamber was closed except for manipulations and examinations, to maintain temperature and humidity.

The appropriate number of eyes (approximately nine to twelve) was selected, after being placed in the superfusion apparatus they were examined again with the slit lamp microscope to ensure that they were in good condition. The focus was adjusted to clearly see the

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physiological saline which was flowing on the cornea surface. Eyes with a high baseline fluorescein staining (i.e. > 0.5) or corneal opacity score (i.e. > 0.5) were rejected. The cornea thickness was measured with an optical pachymeter on a slit-lamp microscope. Any eye with cornea thickness deviating by more than 10 % from the mean value for all eyes, or eyes that showed any other signs of damage were rejected and replaced. If the selected eyes were appropriate for the test, acclimatization was started and conducted for approximately 45 to 60 minutes. The chambers of the superfusion apparatus were at controlled temperature (32±1.5°C) during the acclimatization and treatment periods.

3.6.4 Identification

The eyes were identified by chamber number, marked on the door of the chamber.

3.6.5 The base line assessments

At the end of the acclimatization period, a zero reference measurement was recorded for cornea thickness and opacity to serve as a base line (t=0) for each individual eye. The cornea thickness of the eyes should not change by more than 5% between the -45 min and the zero time. Slight corneal thickness changes (0.0 – 1.6%) were observed in the eyes, this is considered normal when maintaining enucleated eyes. Following the equilibration period, the fluorescein retention was measured. Base line values were required to evaluate any potential test item related effect after treatment. All eyes were considered to be suitable for the assay.

3.6.6 Treatment

After the zero reference measurements, the eye in its retainer was taken out of the chamber and placed on a layer of tissue with the cornea facing upwards. The eye was held in horizontal position, while the test item was applied onto the centre of the cornea.

The test item was applied in a volume of 30 µL onto the entire surface of the cornea attempting to cover the cornea surface uniformly with the test substance, taking care not to damage or touch the cornea.

The positive control eyes were treated in a similar way with 30 µL benzalkonium chloride solution 5 % (w/v). The negative control eye was treated with 30 µL of physiological saline (Salsol solution 0.9 %).

3.6.7 Test item removal

The time of application was observed, then after an exposure period of 10 seconds from the end of the application, the cornea surface was rinsed thoroughly with 20 mL physiological saline at ambient temperature, taking care not to damage the cornea but attempting to remove all residual test item if possible. The eye was returned to the chamber after rinsing. The time while the eye was out of the chamber was limited to the minimum required.

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3.6.8 Observation and assessment of corneal effects

The negative and positive control eyes and all test eyes were evaluated pre-treatment and at approximately 30, 75, 120, 180 and 240 minutes after the post-treatment rinse.

Corneal thickness and corneal opacity were measured at all time points. Fluorescein retention was measured on two occasions, at base line (t=0) and approximately 30 minutes after the post-treatment rinse. A Haag-Streit BP 900® slit-lamp microscope was used for the measurements.

The effects were divided into four categories:
I = none
II = slight
III = moderate
IV = severe

3.6.9 Storage of corneas

At the end of the procedures, the corneas were carefully removed from the eyes and placed individually into labelled containers of preservative fluid (10% neutral buffered formalin) for potential histopathology and stored.

3.7 Evaluation

The endpoints evaluated were corneal opacity, swelling and fluorescein retention. Other observations which indicate damage, such as loss of epithelium can be taken into account in making a classification.

Results from corneal swelling, opacity and fluorescein retention were evaluated separately to generate an Isolated Chicken Eye (ICE) class for each endpoint. The ICE classes for each endpoint were then combined to generate an Irritancy Classification for each test substance (see Table 4).

3.7.1 Corneal thickness or swelling determination

Corneal swelling was determined from corneal thickness measurements made with an optical pachymeter on a slit-lamp microscope. It was expressed as a percentage and was calculated from corneal thickness measurements according to the following formulae:

$$CS \text{ at time } t = \frac{CT \text{ at time } t - CT \text{ at } t=0}{CT \text{ at } t=0} \; x100$$

$$Mean \; CS \text{ at time } t = \frac{FECS_{(at\ time\ t)} + SECS_{(at\ time\ t)} + TECS_{(at\ time\ t)}}{3}$$

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CS = cornea swelling
CT = cornea thickness
$FECS_{(at\ time\ t)}$ = first eye cornea swelling at a given time-point
$SECS_{(at\ time\ t)}$ = second eye cornea swelling at a given time-point
$TECS_{(at\ time\ t)}$ = third eye cornea swelling at a given time-point

Note: For the calculation of Maximum Swelling, small negative numbers for swelling (0 to -5%) following application are counted as zero (scored as class I). Large negative numbers (>12% below control) are probably due to erosion and indicate a severe effect (scored as IV). Cases of values of -5% to -12% are evaluated on a case by case basis but in the absence of other findings do not indicate a severe effect.

Corneal swelling was classified by the following scale:

Mean cornea swelling [%]	ICE Class
0 to 5	I
>5 to 12	II
>12 to 18 (>75 min. after treatment)	II
>12 to 18 (≤75 min. after treatment)	III
>18 to 26	III
>26 to 32 (>75 min. after treatment)	III
>26 to 32 (≤75 min. after treatment)	IV
>32	IV

The four categories are:

	ICE Class
• No swelling	**I**
• Slight swelling	**II**
• Moderate swelling	**III**
• Severe swelling	**IV**

3.7.2 Corneal opacity determination

Corneal opacity was scored using the area of the cornea that was most densely opacified. Corneal opacity was calculated according to the following formulae:

$$\Delta CO \text{ at time } t = CO \text{ at time } t - CO \text{ at } t=0$$

$$Mean\ \Delta CO_{max} = \frac{FECO_{max(30min\ to\ 240min)} + SECO_{max(30min\ to\ 240min)} + TECO_{max(30min\ to\ 240min)}}{3}$$

Remark:
CO at time t = cornea opacity at (30, 75, 120, 180 and 240) minutes after the post-treatment rinse

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CO at t=0 = base line cornea opacity
ΔCO at time t = difference between cornea opacity at t time and cornea opacity base line
FECO = first eye cornea opacity
SECO = second eye cornea opacity
TECO= third eye cornea opacity
$_{max(30min\ to\ 240min)}$ = maximum opacity of the individual eye at 30 to 240 minutes minus base line cornea opacity of the individual eye

Using the mean value of the individual highest opacity scores (mean ΔCO_{max}), an overall maximum opacity score was given for the test item:

- No opacity **0**
- Very faint opacity **0.5**
- Scattered or diffuse areas, details of iris clearly visible **1**
- Easily discernible translucent area, details of iris slightly obscured **2**
- Severe cornea opacity, no specific details of iris visible, size of pupil barely discernible **3**
- Complete cornea opacity, iris invisible **4**

Corneal opacity is classified by the following scale:

Mean maximum opacity score	ICE Class
0.0 - 0.5	I
0.6 - 1.5	II
1.6 - 2.5	III
2.6 - 4.0	IV

The four categories are:

	ICE Class
• No opacity	**I**
• Slight opacity	**II**
• Moderate opacity	**III**
• Severe or total opacity	**IV**

3.7.3 Fluorescein retention determination

Fluorescein retention change was calculated according to the following formulae:

$$\Delta FR \text{ at time } t = FR \text{ at time } t - FR \text{ at } t=0$$

$$Mean\ \Delta FR = \frac{FEFR_{(30min)} + SEFR_{(30min)} + TEFR_{(30min)}}{3}$$

Remark:

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FR at time t = fluorescein retention at 30 minutes after the post-treatment rinse
FR at t=0 = base line fluorescein retention
ΔFR at time t = difference between fluorescein retention at t time and fluorescein retention base line
FEFR = first eye fluorescein retention at 30 minutes after the post-treatment rinse minus base line fluorescein retention
SEFR = second eye fluorescein retention at 30 minutes after the post-treatment rinse minus base line fluorescein retention
TEFR = third eye fluorescein retention at 30 minutes after the post-treatment rinse minus base line fluorescein retention

The mean fluorescein retention value for all test eyes was used to give the overall fluorescein retention score for the test item:

- No fluorescein retention **0**
- Very minor single cell staining **0.5**
- Single cell staining scattered throughout the treated area of the cornea **1**
- Focal or confluent dense single cell staining **2**
- Confluent large areas of the cornea retaining fluorescein **3**

Fluorescein retention is classified by the following scale:

Mean fluorescein retention score	ICE Class
0.0 - 0.5	I
0.6 - 1.5	II
1.6 - 2.5	III
2.6 - 3.0	IV

The four categories are:

	ICE Class
• No fluorescein retention	**I**
• Slight fluorescein retention	**II**
• Moderate fluorescein retention	**III**
• Severe fluorescein retention	**IV**

3.8 Validity of the Test

The results from all eyes used met the quality control standards. The negative control and positive control results were in good correlation with historic data. This experiment was considered to be valid.

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Historical Control data (updated: 24 September 2015):

Negative Control: Physiological saline (Salsol solution, NaCl 0.9% w/v)

Observation	Min. Value	Max. Value
Maximum corneal swelling at up to 75 min	-3.2 %	3.4 %
Maximum corneal swelling at up to 240 min	-4.8 %	3.4 %
Maximum corneal opacity change	0.00	0.50
Fluorescein retention	0.00	0.50
Number of studies	200	

Positive Control: Benzalkonium chloride 5 % (w/v)

Observation	Min. Value	Max. Value
Maximum corneal swelling at up to 75 min	-8.5 %	27.0 %
Maximum corneal swelling at up to 240 min	-10.7 %	34.8 %
Maximum corneal opacity change	2.50	4.00
Fluorescein retention	1.50	3.00
Number of studies	108	

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4.0 RESULTS AND DISCUSSION

The mean values of the treated eyes for maximum corneal thickness change, corneal opacity change and fluorescein retention change are given below. The conclusion on eye irritancy was based on the OECD guideline 438 quantitative assessments.

Details of data interpretation for overall Isolated Chicken Eye Class are given in Table 4.

4.1 Test Item

Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	-1.0 %	I
Mean maximum corneal swelling at up to 240 min	-2.1 %	I
Mean maximum corneal opacity change	0.00	I
Mean fluorescein retention change	0.00	I
Other Observations	None	
Overall ICE Class	3xI	

Based on this *in vitro* eye irritation study in isolated chicken eyes with isopyrazam/difenoconazole SC (A21295D) the test item is considered to be non-irritant.

4.2 Positive Control

Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	9.4 %	II
Mean maximum corneal swelling at up to 240 min	27.8 %	III
Mean maximum corneal opacity change	4.00	IV
Mean fluorescein retention change	3.00	IV
Other Observations	Loosening of epithelium was observed in all eyes (3/3) at 75 minutes after the post-treatment rinse.	
Overall ICE Class	1xIII 2xIV	

The positive control benzalkonium chloride 5 % (w/v) was classed as severely irritating.

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4.3 Negative Control

Observation	Value	ICE Class
Mean maximum corneal swelling at up to 75 min	0.0 %	I
Mean maximum corneal swelling at up to 240 min	0.0 %	I
Mean maximum corneal opacity change	0.00	I
Mean fluorescein retention change	0.00	I
Other Observations	None	
Overall ICE Class	3xI	

The negative control Physiological saline (Salsol solution, NaCl 0.9% w/v) was classed as non-irritant.

5.0 CONCLUSIONS

Under the conditions of this *in vitro* eye irritation study in isolated chicken eyes, isopyrazam/difenoconazole SC (A21295D) is concluded to be non-irritant.

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TABLES SECTION

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TABLE 1 Individual Data for Test Item Isopyrazam/Difenoconazole SC (A21295D)

Study Code:	15/419-038CS														Strain:	ROSS 308									
Date of Exposure:	03 November 2015														Test Item:	Isopyrazam/Difenoconazole SC (A21295D)									
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
12	63	63	0.0%	63	*0.0%*	63	*0.0%*	*0.0%*	63	*0.0%*	63	*0.0%*	62	*-1.6%*	*-1.6%*	0	0	0	0	0	0	*0.0*	0	0	*0.0*
13	63	63	0.0%	62	*-1.6%*	62	*-1.6%*	*-1.6%*	62	*-1.6%*	62	*-1.6%*	62	*-1.6%*	*-1.6%*	0	0	0	0	0	0	*0.0*	0	0	*0.0*
14	64	64	0.0%	63	*-1.6%*	63	*-1.6%*	*-1.6%*	63	*-1.6%*	62	*-3.1%*	62	*-3.1%*	*-3.1%*	0	0	0	0	0	0	*0.0*	0	0	*0.0*
Mean values:					*-1.0%*		*-1.0%*	*-1.0%*		*-1.0%*		*-1.6%*		*-2.1%*	*-2.1%*							*0.00*			*0.00*

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TABLE 2 Individual Data for the Positive Control, 5 % (w/v) Benzalkonium Chloride solution

Study Code:	15/419-038CS														Strain:	ROSS 308								
Date of Exposure:	03 November 2015														Positive Control:	5 (w/v) % Benzalkonium chloride solution								
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
15	63	64	1.6%	66	*3.1%*	69	*7.8%*	*7.8%*	73	*14.1%*	76	*18.8%*	81	*26.6%*	*26.6%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
16	64	64	0.0%	66	*3.1%*	70	*9.4%*	*9.4%*	74	*15.6%*	77	*20.3%*	82	*28.1%*	*28.1%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
17	63	63	0.0%	67	*6.3%*	70	*11.1%*	*11.1%*	73	*15.9%*	77	*22.2%*	81	*28.6%*	*28.6%*	0	4	4	4	4	4	*4.0*	0	3	*3.0*
Mean values:					*4.2%*		*9.4%*	*9.4%*		*15.2%*		*20.4%*		*27.8%*	*27.8%*							*4.00*			*3.00*

Note: Loosening of epithelium was observed in all eyes (3/3) at 75 minutes after the post-treatment rinse.

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TABLE 3 Individual Data for the Negative Control, Physiological Saline (Salsol Solution 0.9%)

Study Code:	15/419-038CS														Strain:	ROSS 308									
Date of Exposure:	03 November 2015														Negative Control:	Physiological saline (Salsol solution, NaCl 0.9% w/v)									
Chamber number ↓	Corneal thickness (instrument units)														Corneal opacity score								Fluorescein retention		
Relative observation time (min) →	-45	0	Change	30	change at 30	75	change at 75	Max change up to 75	120	change at 120	180	change at 180	240	change at 240	Max change up to 240	0	30	75	120	180	240	Max Δ Opac	0	30	Δ Flu ret
18	62	62	0.0%	62	*0.0%*	62	*0.0%*	*0.0%*	62	*0.0%*	62	*0.0%*	62	*0.0%*	*0.0%*	0	0	0	0	0	0	*0.00*	0	0	*0.00*

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TABLE 4 Assessment of the General *in vitro* Eye Irritancy and Regulatory GHS Classification

The following table is used to identify the probably eye irritancy potential of test items. In the case where the result indicates Non-irritant, or Corrosive/Severely Irritating, then the test item can be classified as one of these two cases. In all other cases the probable level of irritancy can be reported, but a regulatory *in vivo* rabbit eye irritation test is required for regulatory classification and labelling purposes.

UN GHS Classification	**Combinations of the three ICE Classes**
No Category	**3×I** **2×I, 1×II**
No prediction can be made	**Other combinations**
Category 1	**3×IV** **2×IV, 1×III** **2×IV, 1×II*** **2×IV, 1×I*** **Corneal opacity ≥ 3 at 30 min (in at least 2 eyes)** **Corneal opacity = 4 at any time point (in at least 2 eyes)** **Severe loosening of epithelium (in at least 1 eye)**

Remark: *: combinations of categories less likely to occur

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APPENDIX 1 Test Item Data Sheet

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TEST ITEM DATA SHEET

This questionnaire allows us to safely store, handle and properly administer your test substance. All data will be treated as strictly confidential. Please also send a certificate of analysis and material safety data sheet if available.

1. SPONSOR (as defined by GLP)			
SPONSOR		**MANUFACTURER** (if different)	
Company *	Syngenta	**Company ***	
Address *	Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, UK, RG42 6EY	**Address ***	
Contact Person *	Jenny Tellis	**Contact Person ***	
Telephone		**Telephone**	
Fax Number		**Fax Number**	
E-mail *	jenny.tellis@syngenta.com	**E-mail ***	

2. TEST ITEM INFORMATIONS			
Test Item Name * (please use the name should be appeared in study report)	Isopyrazam/Difenoconazole SC (A21295D)		
Substance Classification *	☐ Pharmaceutical ☐ Industrial Chemical ☒ Agrochemical ☐ Other		
Chemical Name * (IUPAC, CAS or synonym)	CGA169374/SYN520453 SC (125/125) A21295D SYN520453 CAS No. 881685-58-1,683777-13-1,683777-14-2 CGA169374 CAS No 119446-68-3		
Batch (Lot) Number *	JHU002-107-007		
Manufacture date * (day-month-year)	29/09/2015	**Expiry (Retest) date *** (day-month-year)	29/09/2017
Molecular Weight (if applicable)		**CAS number** (if available)	
Molecular Formula (if applicable)		**Quantity *** (sent by Sponsor)	10g
Structural Formula (if applicable)			
Purity * (otherwise treated as 100%)			
Composition/Ingredients (if applicable)			

* = *mandatory fields*

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APPENDIX 1 Test Item Data Sheet (continued)

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3. PHYSICAL PROPERTIES, STABILITY AND SOLUBILITY INFORMATION			
Colour *	Off white	**Appearance *** (at Room Temperature)	Homogenous, liquid suspension.
Other known parameters (e.g. density, pH value, melting point, boiling point, hygroscopic properties)			
Known analytical methods			
Solubility properties (please mark with X if test item soluble in listed solvents)	☐ Water ☐ 1% Aq. Carboxymethyl cellulose ☐ Acetone ☐ DMSO		
	☐ Ethanol ☐ Propylene glycol ☐ Olive oil ☐ Acetonitrile ☐ DMF		
	☐ Unknown ☐ Other:		

4. HAZARDS INFORMATION (if no MSDS available)				
☐ Explosive	☐ Oxidizing	☐ Flammable	☐ Toxic	☐ Dangerous for the environment
☐ Corrosive	☐ Harmful	☐ Irritant	☐ Unknown	☐ Other:

5. STORAGE (recommended conditions for storage over prolonged periods of time)			
Storage conditions * (please mark with X)	☒ Controlled Room Temperature (15-25°C, below 70 RH%)		
	☐ Refrigerator (2-8°C)	☐ Freezer (≤-15°C)	☐ Ultra Freezer (≤-70°C)
If no information provided, substance will be **stored at controlled room temperature in a dark storeroom.**	☐ Protected from light	☐ Protected from humidity	☐ Under inert gas
	☐ Other, specified here:		

6. DISPOSAL (if no information provided, test item will be disposed after finalisation of all studies)
Remaining Test item * (please mark with X) ☒ Dispose (after finalisation of all studies or 3 months after sending the draft reports) ☐ Return (sample will be returned as "sample without value")
CiToxLAB Hungary Ltd. will retain a reference sample per test item. Returning test item will be at the expense of the Sponsor. Standard freight charges available on request. If additional charges are applicable the Sponsor's agreement will be obtained prior to dispatch. Test item will be send back after sending out the final report(s).

General Remarks			
Signature of Sponsor *	Claire Guiot	**Date *** (day-month-year)	15/10/2015

* = *mandatory fields*

Delivery Address:
Pharmacy Department
CiToxLAB Hungary Ltd.
H-8200 Veszprem, Szabadsagpuszta,
HUNGARY
Phone: +36 88 545 300
Fax: +36 88 545 301
E-mail: dispensary@hu.citoxlab.com

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APPENDIX 2 GLP Certificate

OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

Note: Translation of the Stamp on the official document ("Országos Gyógyszerészeti és Élelmezés-egészségügy Intézet"): ("National Institute of Pharmacy and Nutrition")

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